Beta blockers as cardioprotective agents: Part II—Focus on prevention of sudden cardiac death

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The benefits of beta blocking agents span a wide spectrum of patients who are at risk for major cardiovascular events and sudden death. Data from several large clinical trials show attenuation of risk with beta blocker use in patients with hypertension, myocardial infarction (MI), ischemic heart disease, left ventricular dysfunction, and heart failure. These agents have been shown to improve cardiac performance, reverse cardiac remodeling, reduce hospitalizations, and improve survival in various patient subgroups. The benefits of beta blockade in the treatment of hypertension and after MI have been obvious since the early 1980s.

Sudden cardiac death, the most common consequence of cardiac disease, remains an important public health problem. More than 60% of deaths caused by cardiac disease can be attributed to sudden cardiac death.[1] Much of the benefit conferred by beta blockade can be attributed to the prevention of sudden cardiac death; the reduction in total mortality observed with beta blockers in patients with hypertension, MI, and heart failure is primarily the result of a decrease in sudden cardiac death. Beta blockers are the only class of agents proved to reduce sudden death in these patient populations. Even the angiotensin-converting enzyme (ACE) inhibitors, which are considered the cornerstone of therapy for heart failure, have had little effect on sudden death in clinical trials, except for the Trandolapril Cardiac Evaluation Trial.[2]

In its report on sudden cardiac death, the European Society of Cardiology (ESC) advised that beta blockers be considered mandatory in the prophylactic treatment of acute MI, after MI, and in patients with chronic heart failure.[3] The ESC further states that most of the data in these populations come from investigations of lipophilic beta blockers. This article will summarize the clinical evidence supporting the cardiovascular protective efficacy of beta blockers, with a detailed description of these agents' ability to reduce the risk of sudden cardiac death.

Epidemiology of sudden cardiac death

Patients with coronary artery disease (CAD), myocardial ischemia, cardiac arrhythmias, or hypertension have a high risk of sudden cardiac death, usually caused by the onset of ventricular tachycardia and rapid progression to ventricular fibrillation. In 1998, CAD accounted for 62% of sudden cardiac deaths.[1] More than 60% of cases of ambulatory sudden cardiac death are caused by ventricular fibrillation; 16.5% are caused by bradyarrhythmia, 12.7% by torsade de pointes, and 8.3% by primary ventricular tachycardia.[4]

Asymptomatic persons with several risk factors for CAD are at risk for sudden cardiac death; this risk is even greater for persons with documented CAD. Risk factors include male sex, increasing age, family history of CAD, dyslipidemia, hypertension, smoking, and diabetes mellitus. Those at greatest risk have a history of MI, ischemia, impaired left ventricular function, and ventricular arrhythmias. Diabetes mellitus and hyperglycemia have also been found in some studies to predict sudden cardiac death, although other studies showed an association between diabetes and sudden cardiac death only in patients with CAD.

Beta blockers in hypertension

In the 1980s, primary prevention trials of beta blocking agents in patients with hypertension showed reductions in nonfatal MI and total and coronary mortality. Large-scale studies, such as the Medical Research Council Primary Prevention Trial for Mild Hypertension and the Heart Attack Primary Prevention in Hypertension study found similar prevention of hypertensive complications with diuretics and beta blockers.[5] The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study found metoprolol to be superior to thiazide diuretics in preventing CAD events.[6,7] After a median of 4.2 years of treatment, total mortality was reduced by 48% in patients taking metoprolol compared with those

taking diuretics. A marked reduction in sudden death was apparent in patients treated with beta blockers who participated in the MAPHY or British Medical Research Council studies.

Hypertension increases the risk of sudden cardiac death, mainly through its causal association with left ventricular hypertrophy. The risk of sudden cardiac death in patients with electrocardiographic evidence of left ventricular hypertrophy is similar to that in patients with CAD or heart failure.[8] In the Framingham study, increases in left ventricular mass increased the hazard ratio for sudden cardiac death.[9]

As a result of these impressive findings, the Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has continued to recommend beta blockers along with thiazide diuretics as preferred first-line agents for the treatment of hypertension.[10]

Beta blockers after MI

The benefits of beta blockade in ischemic heart disease suggest that the anti-ischemic effect of beta blocking agents contributes to improved outcomes. Beta blockers also favorably alter the electrophysiologic properties of myocytes and decrease the frequency and complexity of venticular premature beats and thereby reduce the risk of life-threatening arrhythmias. These and other potential mechanisms of beta blockers probably work collaboratively to reduce the risk of coronary events.

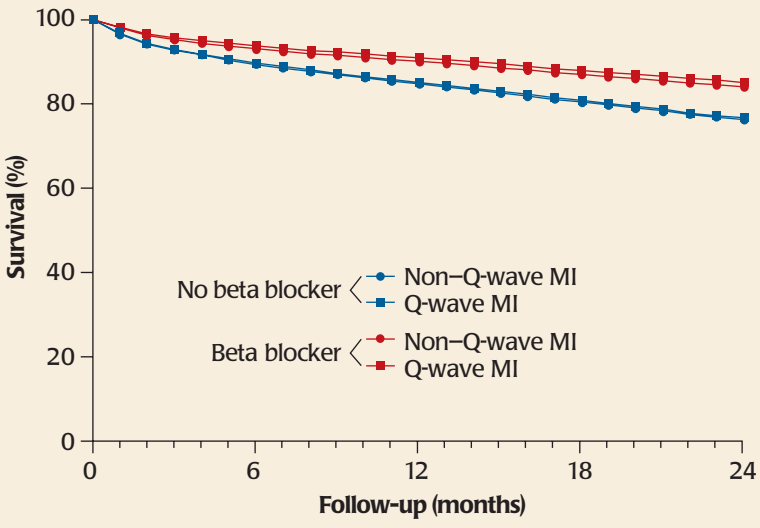
In 1981, the results of three large placebo-controlled studies, the Norwegian Multicenter Study, the Beta Blocker Heart Attack Trial, and the Göteborg Metoprolol Trial, demonstrated convincingly that beta blockers reduced mortality when used after MI.[11-13] In the years since, substantially more data on the ability of beta blockers to reduce death after MI were collected; evidence now exists from more than 50 controlled randomized trials that included more than 55,000 patients. In all studies of beta blockers after MI, the reduction in the risk of mortality was greatest in patients who were at the highest risk for total mortality and sudden cardiac death. In patients with diabetes or heart failure, the reductions in mortality with beta blocker use approached 50%.

Recently, the Cooperative Cardiovascular Project (CCP) database demonstrated a similar effect of beta blockade among high-risk and low-risk patients after MI.[14] The CCP contains data on 201,752 patients with acute MI. Patients who were prescribed any beta blocker at any dose at discharge were classified as having received a beta blocker. The analysis revealed that even low-risk patients benefit from beta blockade after MI; patients with MI and no other complications who were taking beta blockers had a 40% lower mortality than those not taking these agents. The relative risk of death in patients with non–Q-wave MI who were taking beta blockers was also decreased by 40% (Figure 1). Diabetic patients taking beta blockers after MI had a 36% reduction in mortality; those with pulmonary disease and those with heart failure both had a 40% risk reduction.

The CCP database was also used to compare the effects of three beta blockers on survival after MI.[15] The 2-year mortality rates associated with the two beta$_1$-selective agents studied—metoprolol and atenolol—were nearly identical (13.5% and 13.4%, respectively). Survival with all three drugs was superior to that of the group not taking beta blockers, who had a 2-year mortality rate of 23.9% (Figure 2). Although patients with left ventricular dysfunction or clinical heart failure were generally excluded from prospective

FIGURE 1

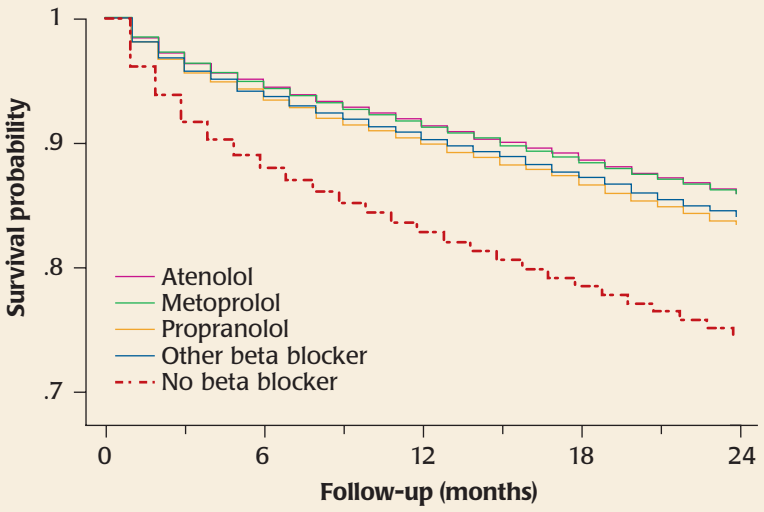
Adjusted probability of survival in patients with Q-wave and non–Q-wave MI who were taking or not taking beta blocker therapy



MI = myocardial infarction.
Reprinted with permission from Gottlieb SS, McCarter RJ, Vogel RA, et al.[14]

FIGURE 2

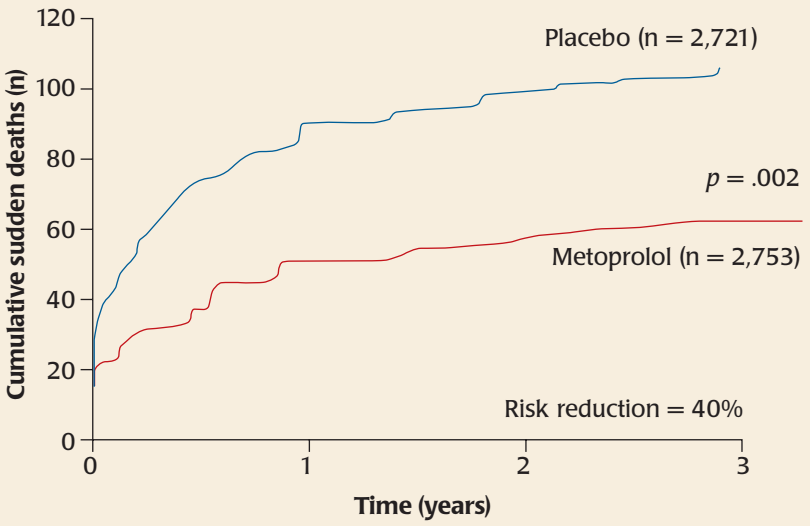
Adjusted mortality of patients taking different beta blockers after MI*



MI = myocardial infarction.
*There were no differences in mortality between patients taking atenolol and metoprolol, and the worse survival of patients taking propranolol is less than that seen in the unadjusted analysis. Patients taking any beta blocker had a much better outcome than those not taking a beta blocker.
Reprinted with permission from Gottlieb SS, McCarter RJ.[15]

FIGURE 3

Cumulative sudden deaths in patients taking placebo and metoprolol in secondary prevention studies



Source: Kendall MJ, et al.[17]

trials of beta blockers after MI, retrospective subgroup analysis of the Beta Blocker Heart Attack Trial demonstrated a significant benefit in post-infarction patients associated with acute MI.[16]

Fatal cardiac arrest may be caused by cardiac arrhythmia in patients with acute thrombotic occlusion of a coronary artery, or by a repeat infarction or new episode of ischemia in a patient with a history of MI. A meta-analysis of data from five studies of patients after MI revealed a highly significant reduction in the incidence of sudden death in patients treated with metoprolol compared with placebo (Figure 3).[17]

Based on the overwhelming evidence supporting the mortality benefits of beta blockade after MI, the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend that beta blockade be initiated at 5 to 28 days in all patients after MI and in those with acute ischemic syndrome and continued indefinitely.[18] Despite these recommendations and the strong evidence to support beta blocker use after MI, the CCP data, which were collected from 1994 to 1995, revealed that only 34% of patients who had an MI were receiving a beta blocker at the time of hospital discharge.[14]

Left ventricular dysfunction and heart failure

Reduced left ventricular ejection fraction is an important risk factor for sudden cardiac death. Left ventricular ejection fraction predicted 2-year all-cause, cardiac, and arrhythmia mortality in a meta-analysis of patients who had survived at least 45 days after MI.[19] Arrhythmia mortality ranged from 3.2% in patients with ejection fractions of 31% to 40%, to 9.4% in patients with ejection fractions of less than 20%. In MI survivors with ejection fractions less than 40%, total mortality is about

20% and sudden cardiac death approaches 10% at 3.5 years.[20]

The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study was undertaken to investigate the long-term effect of beta blockade on morbidity and mortality in patients with left ventricular dysfunction after an MI, with or without heart failure.[21] The study included 1,959 patients with a proven acute MI and an ejection fraction of 40% or less who were randomized to carvedilol or placebo. Carvedilol therapy was associated with a 49% reduction in the combined end point of all-cause mortality and nonfatal MI ($p = .014$) and a 23% reduction in all-cause mortality ($p = .031$). An echocardiographic substudy of CAPRICORN patients revealed that those taking carvedilol had improvements in left ventricular remodeling, consistent with beta blockade's beneficial effects in chronic heart failure.

In CAPRICORN, the end point of sudden death was reduced by 26% in the patients randomized to carvedilol, but this reduction did not reach statistical significance. Much of the reduction in mortality associated with beta blocker use in chronic heart failure can be explained by a reduction in sudden death. The lipophilic beta blockers have been shown to be particularly effective in reducing the risk of sudden death.

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) was a study of 3,991 patients with New York Heart Association (NYHA) functional class II to IV heart failure and an ejection fraction of 40% or less despite optimal standard therapy for heart failure.[22,23] The patients were randomized to extended-release metoprolol succinate (metoprolol CR/XL) or placebo. Metoprolol was started at 12.5 or 25.0 mg daily and titrated at 2-week

Underuse of beta blockers

Despite overwhelmingly positive reports on the use of beta blocking agents in heart failure, recent data indicate that beta blockers account for only 10% of all product usage for heart failure patients when treated by office-based physicians (Figure).[1] Physicians may fail to prescribe beta blockers for patients with heart failure because of the previous concept that they have a negative inotropic effect. We now know that this effect is transitory and, even in severe heart failure, can be overcome with diuretics and a low initial dose. During long-term therapy, there is actually a reversal of remodeling and an increase in ejection fraction. Chronic sympathetic nervous system activation, however, contributes to the progression of heart failure and increases myocardial demand for oxygen. Beta blockers should therefore be used as early as possible in patients with impaired ventricular function. Results from the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial indicate that beta blockade is highly effective in reducing morbidity and mortality in patients with left ventricular dysfunction after MI.

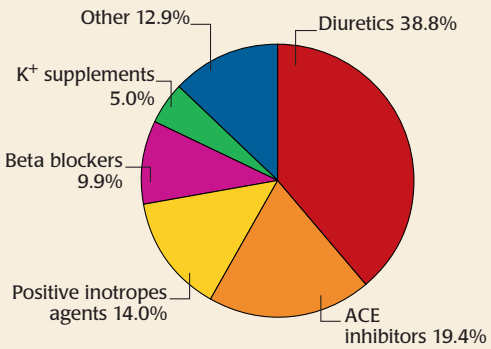
Diabetes mellitus has long been thought to be a contraindication for beta blocker use in patients with heart failure. Recent trials, however, demonstrate that patients with diabetes and heart failure respond at least as well to beta blockade as patients without diabetes.

The same underuse of beta blockers occurs in MI. Studies in the 1990s derived from the CCP database revealed that only about 34% of eligible patients had beta blockers prescribed at the time of discharge, with significant geographic variations in use. Outpatient data show even lower use of beta blockers after MI, with rates as low as 15% in some studies.

As with heart failure and MI, beta blockers may be underused in the treatment of hypertension. Recent data suggest that beta blockers are used in only 22% of hypertension office visits, compared with 27% for calcium antagonists and 31% for ACE inhibitors.[1] Proper treatment of heart failure, MI, and hypertension requires that physicians stay informed about current clinical data and provide proven effective therapies to reduce the incidence of morbidity and mortality in patients with these diseases.

FIGURE

Medication use in congestive heart failure



ACE = angiotensin-converting enzyme.

[1]*Source:* Physician Drug & Diagnosis Audit (PDDA), Scott-Levin, Inc., MAT February 2002.

intervals over 8 weeks until a target dose of 200 mg once daily or the maximum tolerated dose was reached. MERIT-HF was terminated early at the recommendation of the independent end point committee when an interim analysis showed that the preplanned reduction in risk of total mortality was reached.

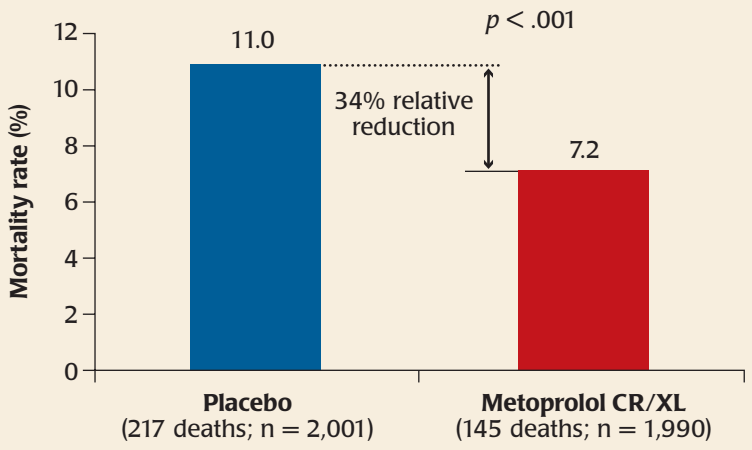
At a mean follow-up of 1 year, the primary end point of all-cause mortality was reduced by 34% in patients taking metoprolol CR/XL (p = .006; Figure 4). The combined end point of total mortality and all-cause hospitalization was reduced by 19%, and total mortality or hospitalization due to worsening heart failure was reduced by 31%, in patients taking metoprolol CR/XL. The rates of other prespecified combined end points were also reduced with metoprolol CR/XL (Figure 5). Beta blocker therapy was associated with a reduction in the total number of days in the hospital due to worsening heart failure.

In MERIT-HF, metoprolol CR/XL was associated with a 41% reduction in sudden death (p < .001). Nearly 60% of the patients who died in MERIT-HF had sudden death as the cause. Sudden death was more common among patients with NYHA functional class II heart failure, who constitute the largest portion of heart failure patients, than in patients with more severe forms of heart failure.

In the second Cardiac Insufficiency Bisoprolol Study (CIBIS II), 2,647 heart failure patients were randomized to bisoprolol or placebo.[17,24] This study was also terminated early based on the profound survival advantage observed in the active treatment group. After a mean follow-up of 1.3 years, all-cause mortality was reduced by 34% (p < .001) in the patients taking bisoprolol. The survival advantage associated with bisoprolol in CIBIS II was most robust in patients with mild-to-moderate heart failure. Bisoprolol also reduced the risk of sudden death by 44% (p = .001). Similarly, favorable effects on the risk of sudden death have been reported in trials of carvedilol.

FIGURE 4

Total annual mortality rate in patients taking metoprolol CR/XL compared with placebo in MERIT-HF



MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.
Source: MERIT-HF Study Group.[22]

In heart failure, most sudden deaths can be attributed to ventricular fibrillation. Metoprolol CR/XL was shown to decrease the frequency of nonsustained ventricular tachycardia and couplets in patients with heart failure.[25] Thus, an antiarrhythmic and antifibrillatory effect of beta blockers may explain their efficacy in preventing sudden death, although an interplay of mechanisms may be possible. Another explanation for the striking reduction in sudden death with beta blockers may be their favorable impact on cardiac remodeling.

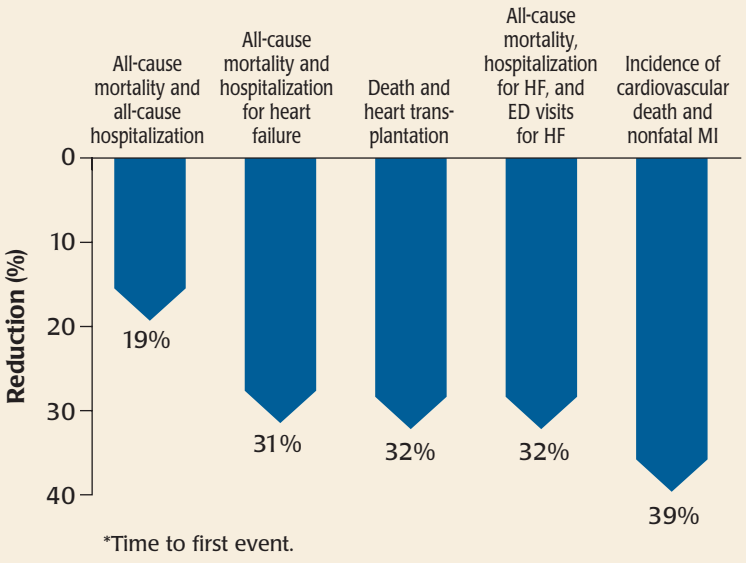
The favorable effects of beta blockade in heart failure have been observed in various subgroups examined. In MERIT-HF, men and women alike benefited from long-acting metoprolol CR/XL treatment, although only one third of the study participants were women. Older and younger heart failure patients also derived benefit, as did diabetic and nondiabetic patients and those with heart disease of ischemic or nonischemic origin. In the U.S. Carvedilol Heart Failure Program, morbidity and mortality were reduced to a similar degree with carvedilol in patients with ischemic heart disease or nonischemic dilated cardiomyopathy, and in patients with or without CAD.[26]

Adding a beta blocker to low to intermediate doses of an ACE inhibitor appears to have a greater effect on reducing the risks of death and hospitalization than does increasing the dose of ACE inhibitor to the maximally tolerated dose, according to an analysis by Packer.[27,28]

In their most recent practice guidelines for the prevention and treatment of heart failure, the AHA and the ACC recommend that beta blocking agents be administered to patients with acute MI because they have been shown to reduce the risk of reinfarction or death when initiated soon after the ischemic event,

FIGURE 5

Benefits of metoprolol CR/XL on combined end points* in MERIT-HF



HF = heart failure; ED = emergency department; MI = myocardial infarction.
MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.
Source: Hjalmarson A, et al.[23]

especially in patients whose course is complicated by heart failure.[29] Beta blockers are also recommended for patients with a recent MI and preserved left ventricular function. The guidelines also suggest the use of beta blockers in asymptomatic patients with low ejection fraction, especially those with CAD. Routine use of beta blockers in the management of heart failure is also recommended to lessen symptoms and improve clinical status.

The AHA/ACC heart failure guidelines note that the benefits of beta blockers are observed in patients with or without CAD and with or without diabetes, and are additive to the benefits of ACE inhibitors. Even patients who have mild symptoms or appear to be clinically stable have a high risk of mortality and should receive early treatment with beta blockade. In patients with little disability from their heart failure, beta blockers reduce the risk of disease progression, clinical deterioration, and sudden death.

Conclusion

Beta blocking agents are considered first-line agents for the treatment of hypertension based on their ability to prevent CAD events in the hypertensive population. Data demonstrate convincingly that beta blockers should also be used routinely to reduce the risk of mortality in all patients after MI who have no contraindications. The most recent findings indicate that beta blockers are associated with impressive reductions in mortality, progression of disease, and the rate of hospitalizations in patients with heart failure of varying severity.

Initiation of beta blockade early in the course of heart failure, even in patients without symptoms, reduces the risk of clinical deterioration and death. New data reveal that patients with left ventricular dysfunction experience morbidity and mortality benefits from beta blockers after MI. Much of the mortality benefit conferred by beta blockade in these diseases can be attributed to prevention of sudden cardiac death. ■

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